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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,185	12/26/2000	Gilles Philippus van Wezel	4666US	6157

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,185	VAN WEZEL ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,8,9,11,14-19,29-33 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8,9,11,14-19,29-33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-28-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 8-9, 11, 14-19, 29, 30-33, 35 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 9-28-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the previous rejections under 35 U.S.C. 102(b) and 103(a) in view of claim amendments. However, new rejections are in place.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 35 recites a method of producing a recombinant bacterium which method comprises simply "providing" said bacterium with a polynucleotide. The scope of the word "providing" is not clear to the Examiner. Furthermore, simply providing a bacterium with a polynucleotide will not render said bacterium recombinant as opposed to "transforming or transfecting" wherein a set of conditions are applied. Therefore, it is not clear to the Examiner as to how those skilled in the art can achieve the results of said method claimed in claim 35.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a recombinant actinomycete by transforming said actinomycete such as *Streptomyces* lacking a detectable endogenous SsgA using the polynucleotide with SEQ ID NO:1 encoding a polypeptide with SEQ ID NO:3 for enhancing septation and fragmentation of said bacterium, does not reasonably provide enablement for such a method using any or all means (i.e., any DNA). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 30 so broad as to encompass the use of any means or any DNA having the capability to encode any protein and isolated from any source or derived from any source including derivatives, variants, mutants and recombinants in the above method. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA sequences that are broadly encompassed by the claims.

Applicants propose to use the above polynucleotides for the process of making transformants with a specific phenotypical characteristic. Since the nucleotide sequence determines the type of protein and the ultimate function of the encoded protein and thereby the phenotype of the transformant changing or using any means (i.e., any nucleotide sequence) as proposed by the applicants and/or addition of substantial amount of additional nucleotide sequence unrelated to the nucleic acid sequence of SEQ ID NO:1 may not lead to desired function of said means (i.e., said polynucleotides). This is because the changes suggested by the applicants will result in the use of an enormous number of nucleotide sequences that may or may not have the desired function. However, in this case the disclosure is limited to the use of a single nucleotide sequence with SEQ ID NO:1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or modifications of nucleotides, as encompassed by the instant claims, and the base changes within a nucleic acid's sequence can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given DNA to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA from any source because the specification does not establish: (A) a rational and predictable scheme for transforming an actinomycete bacterium using any or all means; (B) the general tolerance of ssgA DNA sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any DNA with an

expectation of obtaining the desired biological function and utility; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of any DNA or its derivative or fragment as having the above property. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of DNAs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous rejection applicants traverse. Applicants argue that as stated in the MPEP, 35 U.S.C. 112, sixth paragraph states that a claim limitation expressed in means-plus-function language shall be construed to cover the corresponding structure...described in the specification and that means or step plus function limitation should be interpreted in a manner consistent with the specification disclosure. While that may be so, such an argument is not persuasive to overcome the above rejection. That is because, the means-plus-function language recited in the above claim is not just limited to the method disclosed in the disclosure but reads on all or any means for which there is no support in the disclosure. Contrary to applicant's argument, claim 30 continues to be directed to a method of using "any DNA" or any means or all means to transform an actinomycete bacteria, for which there is no specific guidance in the specification. Without such guidance one of ordinary skill would be reduced to the necessity of

producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) a rational and predictable scheme for transforming an actinomycete bacterium using any or all means; (B) the general tolerance of ssgA DNA sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any DNA with an expectation of obtaining the desired biological function and utility; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Hence the rejection is maintained.

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim is directed to a method of producing a filamentous bacterium using a genus of polynucleotides that have not been described in the specification.

The specification does not contain any disclosure of the structure of all such "means" (polynucleotides or genes) for enhancing septation and fragmentation. The genus of the "means" is a large variable genus with the potentiality of having different structures. Therefore, many structurally unrelated "means" (i.e., DNAs) are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species, i.e.,

SEQ ID NO:1 of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have traverse the above rejection with a similar argument they made for the enablement rejection. Examiner respectfully disagrees. As discussed in the written description guidelines, the written description requirement for a method of using a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written

description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed method is directed to the use of a genera of DNA (or whatever means) whose species which are widely variant in structure. The genus is structurally diverse as it encompasses polynucleotides and other such agents (means) whose structure is not known. As such, the description of the solely the function of the "means" present in all members of the genus is not sufficient to be representative of the attributes and features of the entire genus. Hence the above rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 8-9, 11, 14-15, 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Kawamoto et al. (Actinomycetologica, 1995, Vol. 9:136-151, cited in Form 1449 dated 12-26-00, also see DNA and amino acid sequence alignment with database GenEmbl Accession No. D50051 and SPTREMBL_19, Accession No. P95753, May 1, 1997). This rejection is based upon the public availability of a printed publication one year before the effective filing date of the instant application. Claims 1, 3, 8-9, 11, 14-15, 30-33 of the instant application are drawn to a method for producing a filamentous recombinant bacterium (exhibiting reduced branching and fragment septation during growth or exhibiting enhanced fragmentation during growth), wherein the method comprises transforming a filamentous bacterium with a heterologous polynucleotide encoding SsgA with SEQ ID NO:3 and wherein such a SsgA isnot present in said Streptomyces

in nature and wherein said Streptomyces bacterium lacks detectable endogenous SsgA activity during submerged culture, and wherein the polynucleotide is integrated into the bacterial genome or is a part of an episomal element, wherein the *ssgA* activity is inducible or repressible with a signal, wherein the filamentous bacterium is an actinomycete such as *Streptomyces lividans* or *S.coelicolor* and wherein the filamentous bacterium produces a useful product such as an antibiotic.

Kawamoto et al. disclose an identical method using a polynucleotide which is 100% identical to SEQ ID NO:1, isolated from *S.griseus*, which when transformed into another actinomycete such as *S. lividans* lacking detectable endogenous SsgA during submerged culture, results in formation of septate form of the bacterium, wherein the polynucleotide is integrated into the genome or resides as an episomal element, wherein the expression of the gene product is inducible and wherein the actinomycete bacterium produces a useful product such as an antibiotic, streptomycin and wherein the polynucleotide encodes a polypeptide comprising SEQ ID NO:3 and wherein the polynucleotide with SEQ ID NO:1 encoding a polypeptide with SEQ ID NO:3 works as a means for enhancing septation and fragmentation of the transformed bacterium and wherein the transformed bacterium is selected from a group which includes *S.lividans*. Thus Kawamoto et al. anticipate claims 1, 3, 8-9, 11, 14-15, 30-33 of this application as written.

In response to the previous Office action, applicants have traversed the above rejection. Applicants have amended claims in by including phrases such as "heterologous SsgA" and arguing that Kawamoto et al. does not anticipate claim 1 since Kawamoto et al. does not disclose each and every element of amended claim 1. Applicants specifically argue that Kawamoto et al.

does not disclose providing a filamentous actinomycete bacterium lacking detectable endogenous SsgA with a heterologous polynucleotide encoding SsgA. Examiner agrees. Therefore, Examiner has withdrawn the previous rejection based on Kawamoto et al., 1997 reference and put in place a new rejection based on another earlier reference of Kawamoto et al., 1995 reference which clearly discloses transformation of *S.lividans* with a heterologous SsgA isolated from *S.gresius* as required to anticipate claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-19, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawamoto et al. as applied to claims 1, 3, 8-9, 11, 14-15, 30-33 above, and further in view of the common knowledge in the art for making recombinant bacterium and expressing heterologous proteins using the same. Claims 16-19 are drawn to a method of making a heterologous protein using the filamentous bacterium produced by the method of claims 1, 3-9, 11, 13-15, 30-33. The method of making heterologous recombinant proteins by transforming host cells is well known in the art of molecular biology. The method of making an actinomycete such as *S.griseus* or *S.lividans* with enhanced septation and fragmentation is taught by Kawamoto et al. Therefore with a strain of filamentous bacterium which undergoes fragmentation thereby increasing its total cell number and in turn increasing the production of any protein that it produces, it would have been

obvious to one of ordinary skill in the art to use such a filamentous bacteria to produce a heterologous protein by transformation techniques. One of ordinary skill in the art would have been motivated to do so as filamentous bacteria which are generally easily cultivated on a larger scale to produce large amounts of heterologous protein when available in fragmented form would be much more amenable for large scale cultivation because it overcomes the problems of clumping of mycelial masses thus allowing better nutrient and oxygen transport resulting in more growth and production of the intended product. One of ordinary skill in the art would have a reasonable expectation of success since Kawamoto et al. provide the technique for making such fragmented bacteria and the art provides techniques for transformation of such cells to produce any heterologous polypeptide by transformation.

Therefore the above claims would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that as Kawamoto et al. does not anticipate claim 1, claims 16-19 depending therefrom remains non-obvious. However, contrary to such a conclusion by the applicant, examiner has now shown that the instant Kawamoto et al. reference does anticipate claim 1 and renders claims 16-19 *prima facie* obvious to those skilled in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

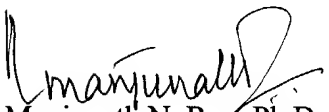
None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization

where this application or proceeding is assigned is 703-872-9306/9307 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

December 2, 2004